UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte HOUSSAM IBRAHIM, MARTINE BAYSSAS, HENRI POURRAT and CHRISTINE DEUSCHEL

Appeal No. 2005-1535
Application No. 10/049,379

ON BRIEF

Before ADAMS, MILLS, and GREEN, Administrative Patent Judges.

MILLS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. §134 from the examiner's final rejection of claims 1-11 and 15-17 which are all of the claims on appeal in this application.

Claim 1 is representative and reads as follows:

1. Oxaliplatinum stable pharmaceutical preparation for parenteral administration, characterized in that the oxaliplatinum is contained in a solution in a solvent at a concentration of at least 7 mg/ml and in that said solvent comprises a sufficient quantity of a hydroxylated derivative selected among 1,2 propanediol, glycerol, maltitol, saccharose and inositol.

The prior art references cited by the examiner are:

Ibrahim et al. (Ibrahim)	5,716,988	Feb. 10, 1998
Schlipalius	5,897,871	Apr. 27, 1999

Grounds of Rejection

Claims 1-11 and 15-17 stand rejected under 35 U.S.C. §103(a) over Ibrahim and Schlipalius.[1]

We reverse this rejection.

DISCUSSION

Background

Oxaliplatinum is a antineoplastic agent used per intravenous administration in particular in the treatment of metastatic colorectal cancers. "[O]xaliplatinum, in form of a pure active substance, is known to be slightly soluble in water, very little soluble in methanol and practically insoluble in ethanol and acetone. More precisely, the maximal solubility of oxaliplatinum saturated in water at 37˚C is of 7[.]9 mg/ml, but at 20˚C it falls down to 6 mg/ml. In methanol at 20˚C, it is only of 0.22 mg/ml." Specification, page 1.

> Recently, a pharmaceutically stable oxaliplatinum preparation, ready to be administrated parenterally by perfusion, constituted by an aqueous solution of oxaliplatinum at a concentration of about 2 mg/ml, and not containing other adjuvants, has been described by Ibrahim and [sic] al. in WO 96104904. .... [T]his preparation was not satisfactory, in particular, because of its oxaliplatinum concentration which was much

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[1] The rejection of the claims over Ibrahim in view of Blackshear, U.S. Patent No. 4,439,181, has been withdrawn. Answer, page 3.

lower than the solubilities mentioned above. This low concentration is required to prevent all risk of precipitates or crystals susceptible to appear, for example, during conservation at low temperatures in a refrigerator or during transport at winter conditions. When such precipitates appear in a pharmaceutical preparation, the hospital staff is generally warned, if there is a doubt, to keep this sample out. If however, a redissolution should be attempted, a heating process at temperatures higher than 40°C,possibly coupled with sonication should be done.

This is why a pharmaceutical preparation based on an oxaliplatinum solution at a concentration of 2 mg/ml, ... needs manipulation of big volumes. For example, the generally recommended dosage during a short perfusion treatment of between 2 and 6 hours, is of 130 mg oxaliplatinum per m^2 body surface. When taking an average body surface of 1[.]7 m^2, it is then advisable to use at least 110 ml of this 2 mg/ml preparation.

One of the aims of the present invention is to make available a stable oxaliplatinum pharmaceutical preparation, for parenteral administration intended to be perfused of [sic] injected, in which the oxaliplatinum concentration would be clearly increased in a way to significantly reduce the volumes to manipulate and/or to use.

Specification, pages 1-2.

[A]lcohols like ethanol and benzyl alcohol, dimethylformamid or dimethylacetamid did not allow, mixed with water, to considerably enhance the solubility of oxaliplatinum. Among the polyalkenes and in particular the polyalkene glycols having a molecular weight between 150 and 6000, only polyethylene glycol allows to enhance considerably the oxaliplatinum solubility. This compound has nevertheless not been retained as possible solvent component because the obtained solution was strongly colored. The crown ethers as some cyclodextrines allowed to enhance very slightly the oxaliplatinum concentration but not sufficiently for the desired applications. Among the carbon hydrates solubilised in water, lactose, sorbitol, solketal, mannitol, amongst others, have shown to be ineffective. Other carbohydrates such as cellobiose, trehalose, melibiose, gentiobiose, raffinose, stachyose or melozitose have shown that, solubilised in water, they allow to dissolve, at least a part of the oxaliplatinum but they are available on the market at a prohibitive price to be used as solvents. A wide range of surfactants, in particular Tween 20, Tween 60 and Tween 80 have shown to be ineffective to make oxaliplatinum soluble.

Obviousness

Claims 1-11 and 15-17 stand rejected under 35 U.S.C. §103(a) over Ibrahim and Schlipalius.

In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. See In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). A prima facie case of obviousness is established when the teachings from the prior art would have suggested the claimed subject matter to a person of ordinary skill in the art. In re Bell, 991 F.2d 781, 783, 26 USPQ2d 1529, 1531 (Fed. Cir. 1993). An obviousness analysis requires that the prior art both suggest the claimed subject matter and provide a reasonable expectation of success to one reasonably skilled in the art. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). With this as background, we analyze the prior art applied by the examiner in the rejection of the claims on appeal.

According to the examiner,

> Ibrahim et al. teach a solution of oxaliplatinum and water for administration through injection of infusion (see reference column 2, lines 9-19). The concentration of the oxaliplatinum is from 1 to 5 mg/ml (col. 2, lines 9-19). The solution can be sealed in a vial infusion pouch, an ampoule or carried in an injection micropump (col. 2, lines 54-63). The method of preparation is recited in Example 1 at Column 3. Ibrahim et al. do not expressly teach the exact concentration for the oxaliplatinurn nor does the reference teach other solvents for the solution.
>
> Schlipalius teaches that active agents can be in solution with glycerol and can be administered by injection or infusion (col. 7, claims 1-5; and col. 3, line 15 - col. 14, line 36).

> At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to use a suitable solvent to prepare injection or infusion solution for administration that includes oxaliplatinum and glycerol in differing concentrations.
>
> While the reference does not teach the complete concentration range, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 105 USPQ 233, 235 (CCPA 1955). The Examiner does not see the criticality in the particular concentrations for oxaliplatinum compound. The prior art teaches the compound to have the same activity in a concentration close of the claimed concentration. Any difference is a matter of degree and not of kind.

Answer, page 4.

Upon review of the Examiner's Answer, we do not find the evidence before us supports a prima facie case of obviousness of the invention, as claimed. In particular, as indicated in the background section above, Ibrahim describes oxaliplatinum in water delivered by the parenteral route in a concentration of 1 to 5 mg/ml. Col. 2, lines 9-18. Schlipalius describes a method and composition for the treatment of melanoma including beta carotenoid and a water soluble dispersible component which may be glycerol. Claims 1-4.

The examiner argues that "[w]hile the reference does not teach the complete concentration range, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical." Answer, page 4. However, the claimed oxaliplatinum concentration of "at least 7 mg/ml" is not "encompassed" by the Ibrahim prior art range

of 1 to 5 mg/ml, and thus Ibrahim is not evidence to support a prima facie case of obviousness of the claimed oxaliplatinum concentration of "at least 7 mg/ml".

Appellants argue that the "concentration range of Ibrahim is **not** close to the claimed range." Reply Brief, page 2. In addition, appellants argue that "the Examiner's Answer does not appreciate or properly recognize that a preparation in a much higher concentration is quite beneficial ... because it significantly reduces the pharmaceutical preparation volumes and administrations. Reply Brief, page 3.

We do not find the examiner has provided evidence of an oxaliplatinum composition having a concentration of 7 mg/ml as claimed, or indicated where the cited references provide one of ordinary skill in the art a reason, suggestion or motivation for combining the cited references to arrive at that concentration.

Appellants argue, "Schilpalius does not describe or suggest any composition or method leading to a pharmaceutically stable preparation of oxaliplatinum as claimed in claim 1 of the subject application. This reference merely describes a method for obtaining a beta-carotene composition in an emulsified form. See, for example, column 5, lines 41-49 and column 5, line 53 to column 6, line 11 of Schilpalius. This disclosure is completely unlike the claimed invention. Moreover, there is no motivation or suggestion in either the primary reference or this secondary reference to combine these two references and end up with the claimed invention." Brief, page 12.

In view of the above, we agree with appellants that the examiner has failed to provide evidence to support a prima facie case of obviousness. Nor does the examiner

provide motivation for combination of the cited references. The examiner has not indicated why one of ordinary skill in the art would have been motivated to incorporate glycerol into an oxaliplatinum composition. In our view, while Schlipalius relates to an intravenous composition comprising glycerol, Schlipalius does not suggest that adding glycerol to oxaliplatinum would increase their concentration or solubility while maintaining shelf life. While Schlipalius may have indicated to one of ordinary skill in the art that beta carotene could be delivered intravenously in glycerol, in view of the solubility spectrum of oxaliplatinum as set forth in the specification, we do not find Schilpalius provides motivation to deliver oxaliplatinum in glycerol or that one of ordinary skill in the art would have been motivated to do so with an expectation of success.

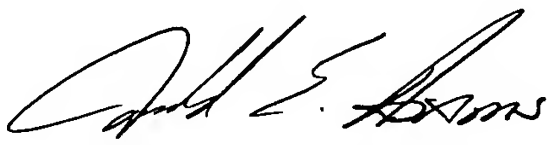
In view of the above, the rejection of the claims for obviousness over Ibrahim in view of Schlipalius is reversed.

CONCLUSION

The rejection of claims 1-11 and 15-17 for obviousness over Ibrahim and Schlipalius is reversed.

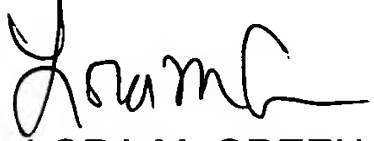
No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

REVERSED



DONALD E. ADAMS
Administrative Patent Judge

DEMETRA J. MILLS
Administrative Patent Judge



LORA M. GREEN
Administrative Patent Judge

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